Version Number: 3	**Research & Development Policy 151-17**	Supersedes Document Dated: N/A
Effective Date: 04/13/2010	**REQUIREMENTS FOR REPORTING RESEARCH EVENTS INVOLVING HUMAN SUBJECT RESEARCH**	Expiration Date: 04/12/2014

I. PURPOSE

This policy describes the types of events (unanticipated problems involving risks to participants or others, serious or continuing non-compliance, or suspension or termination of Institutional Review Board (IRB) approved research) that must be reported to appropriate regulatory agencies, and how such reports are to be prepared and sent.

2. SCOPE

This Policy:

a. Identifies the research events that must be reported to facility research oversight committees,
b. Identifies the research events that must be reported to ORO Northeastern Regional Office,
c. Identifies the research events that must be reported to ORO Central Office,
d. Provides the methods and timelines for reporting such events, and
e. Indicates what information must be provided in reports of these events.

3. DEFINITIONS : See R&D SOP 151-01 Appendix B

4. GENERAL REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO ORO

a. **Applicability.** The reporting requirements of this policy apply only to VA research. Appendix A summarizes the research events that must be reported to ORO.

b. **Facility Director Responsibilities.** The Facility Director is responsible for:

(1) Ensuring standard operating procedures (SOPs) are developed, written, and published providing detailed procedures to ensure the reporting requirements of VHA Handbook 1058.01 are met.

(2) Ensuring all other relevant reporting requirements both within VA and to external agencies and accrediting organizations are satisfied.

(3) Notifying ORO in writing as soon as possible but no later than 5 business days after being informed of a research event under the requirements of this policy. This notification is to be sent to

ORO Northeastern Regional Office, with a copy to the Veterans Integrated Service Network 2 (VISN2) Director.

(a) Although facility representatives are encouraged to contact ORO as soon as a reportable research event is suspected, the Facility Director must provide ORO with a signed, written report of each such event.

(b) A written report from the Facility Director is required whether or not disposition of the event has resolved at the time of the initial report.

(c) Follow-up reports detailing any additional findings and appropriate remedial actions must be provided to the appropriate ORO office at intervals and in a manner specified by that office.

(4) Developing and publishing SOPs that provide detailed procedures on how to ensure compliance in accordance with the requirements of VHA Handbook 1058.01 related to Human Research, Animal Research, Research Safety, Research Laboratory Safety, and Research Information Protection.

(5) Ensuring all other relevant requirements related to reporting research events, both within VA and to external agencies and accrediting organizations are satisfied.

c. **Contents of Reports to ORO.** Reports to ORO of research events must include:

(1) The name and any relevant Assurance number of the reporting VA facility.
(2) The title of the research project(s).
(3) The number(s) used by the facility's IRB to identify the project(s).
(4) The name of any external sponsor(s) of the project(s).
(5) The funding source(s) for the project(s).
(6) A detailed description of the event being reported.
(7) A detailed description of the actions taken (or to be taken) to address the reported event, including systemic actions where warranted.
(8) The name of any agencies or organizations external to VA that were notified, or are to be notified, of the event.

5. REQUIREMENTS RELATED TO HUMAN RESEARCH:

a. **Reports Within the Facility.** The Medical Center Director is responsible for ensuring SOPs are established and published to ensure compliance with the reporting requirements in subparagraphs 5a(1) through 5a(5) of VHA 1058.01.

(1) **Unanticipated Problems Involving Risks to Subjects or Others**. Investigators, RCOs, and other members of the VA research community must report all unanticipated problems involving, or suggesting, risks to subjects or others in VA research to the Associate Chief of Staff for Research (ACOS for R) and the IRB as soon as possible but no later than 5 business days after becoming aware of the problem.

An unanticipated problems involving risks to subjects or others must meet all three of the following criteria;

- The event is unanticipated or unexpected;
- The event is more likely than not related to the research (but not limited to only research procedures);
- The event involves risks to research subjects or others.

(2) Other problems that must be reported include, but are not limited to:

(a) Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.

(b) Any work-related injury to personnel involved in human research, or any research-related injury to any other person, requiring more than minor medical intervention or that leads to serious complications or death.

(c) Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility's research projects.

(d) Any Data Monitoring Committee (DMC) report describing a safety problem.

(e) Any sponsor analysis describing a safety problem. ***NOTE:*** *Sponsor "AE Reports" lacking meaningful analysis are not considered problems.*

(3) **SAEs.** VA investigators must report all local SAEs in VA research to the ACOS for R and the IRB as soon as possible, but no later than 5 business days after the event has become known to the investigator utilizing the Serious Adverse Event Report Form (see subpar. 4c).

(4) **IRB Review of SAEs and Unanticipated Problems Involving Risks to Subjects or Others.** Within 5 business days after a report of an unanticipated problem involving risks to subjects or others or a local SAE, a qualified IRB member-reviewer (or alternatively, the convened IRB) must determine and document whether or not it is anticipated or unanticipated; and whether it is related, possibly related, or probably not related to the research; and whether it involves risk to subjects or others utilizing the Reportable Event Assessment Form. ***NOTE:*** *Appendix B provides information and decision charts related to reporting SAEs and problems involving risks to subjects or others, to the IRB and to ORO.*

(a) The qualified IRB member-reviewer (or the convened IRB) must also document whether or not one of the following applies:

1. Immediate action (e.g., suspension of activities; notification of subjects) is necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii), and review by the convened IRB is needed; or

2. Review by the convened IRB is needed, but immediate action to prevent an immediate hazard to subjects is not warranted. All events determined to be unanticipated problems will be reviewed by the convened IRB.

(b) If the preceding determinations are made by a qualified IRB member-reviewer using the expedited process, the determinations must be reported to the IRB at the IRB's next convened meeting.

(c) If the qualified IRB member-reviewer (or the convened IRB) determines that the problem or AE is unanticipated, related, or possibly related, to the research and involves risks to subjects or others, the IRB Chairperson must report the problem or event to the Facility Director as soon as possible, but no later than 5 business days after the determination. The report must be submitted for convened IRB review.

(d) If it is determined that an informed consent modification is warranted, the convened IRB must determine and document in its records whether or not previously enrolled subjects must be notified of the modification and, if so, when such notification must take place and how such notification must be documented.

(5) **Serious or Continuing Noncompliance**. Members of the VA research community must report the possible noncompliance to the ACOS for R and the IRB within 5 business days of becoming aware of possible serious or continuing noncompliance with VA or other Federal requirements related to human research (e.g., VHA Handbook 1200.5; the Common Rule at 36 CFR 16; Food and Drug Administration (FDA) regulations at 21 CFR 50 and 56) or with IRB requirements or determinations.. ***NOTE:*** *For purposes of this policy, "possible serious or continuing noncompliance" includes all findings of noncompliance related to human research by any VA office, any other Federal department or agency (e.g., FDA), or any other entity.*

(a) If the convened IRB determines that the possible noncompliance is or was serious or continuing, the IRB Chairperson must report the noncompliance to the Facility Director and the R&D Committee as soon as possible, but no later than 5 business days after the IRB's determination, with concurrent notification to the ACOS/R and RCO.

(b) In addition to the requirements in preceding subparagraphs, an RCO identifying serious or continuing noncompliance during an informed consent or regulatory audit must report the noncompliance to the Facility Director, the ACOS for R, the R&D Committee, and the IRB and/or the IACUC as soon as possible but no later than 5 business days after becoming aware of the noncompliance.

(6) **Terminations or Suspensions of IRB Approval.** The IRB Chairperson must report terminations or suspensions of IRB approval of any research related to concerns about the safety, rights, or welfare of human research subjects, research staff, or others to the Facility Director as soon as possible, but no later than 5 business days after the IRB's action.

a. **Reports to ORO ROs.** The Facility Director must report the following research events to the appropriate ORO RO as soon as possible but no later than 5 business days after being informed of them (see App. A).

(1) **Problems in VA Research.** Any problem in VA research that is determined, according to subparagraph 6a(3), to involve serious risks to subjects or others, and be unanticipated and related, or possibly related, to the research.

(2) **AEs.** Any AE in VA research that is determined, according to subparagraph 6a(3), to be serious (i.e., an SAE) and unanticipated and related, or possibly related, to the research.

(3) **Serious or Continuing Noncompliance.** Noncompliance determined by the IRB or identified by an RCO, during an informed consent or regulatory audit, to be serious or continuing.

(a) The Facility Director must simultaneously report serious or continuing noncompliance identified by an RCO, during an informed consent or regulatory audit, to the Director of the VISN, or designee, in which the facility is located and the VHA Chief Research and Development Officer (CRADO), or designee.

(b) Reports based on findings made by entities external to the facility must include a copy of the entity's official findings.

(4) **Terminations or Suspensions of IRB Approval.** Terminations or suspensions of IRB approval of research that are related to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.

b. **Reports to ORO CO.** The Facility Director must report the following research events to ORO CO, with a copy to the appropriate ORO RO, as soon as possible, but no later than 5 business days after being informed of them (see App. A, Table 2).

(1) **Assurance Changes.** Any change in the facility's FWA, or other ORO-approved Assurance.

(2) **IRB Changes.** Any change in the facility's designated IRB(s).

(3) **MOU Changes.** Any change in an MOU with an affiliate institution or other entity related to the designation of IRB(s) or other human research protection arrangements.

(4) **Accreditation Problems.** Failure of the VA facility to achieve the accreditation status required by ORD for human research protections, any change in the facility's accreditation status, or any change in the accreditation status of an affiliate involved in the facility's human research protection program.

6. REQUIREMENTS RELATED TO RESEARCH INFORMATION PROTECTION

a. **Reports Within the VA Facility:** Investigators, RCOs, and other members of the VA research community must report the research events listed in subparagraphs 6.a – 6.e to the ACOS for R as soon as possible, but no later than 5 business days after becoming aware of them. Where applicable, simultaneous reports must be made to the facility Information Security Officer (ISO), Privacy Officer (PO), and/or relevant research oversight committee(s).

(1) In case of loss of VHA sensitive data: **At a minimum,** the following should occur as soon as a loss is discovered

a. Report the loss or theft to security/police officers immediately
b. If you are in a VA facility, notify the VA police (ext. 53333)
c. If you are on travel or at another institution, notify the security/police officers at the institution such as hotel security, university security, etc. as well as the police in the jurisdiction where the event occurred
d. Obtain the case number and the name and badge number of the investigating officer(s). If possible, obtain a copy of the case report.

(2) Immediately call or email the following regarding the incident:

a. Your supervisor
b. Local Information Security Officer (ISO – Barth Brawdy, ext. 54620, Barth.Brawdy@va.gov)
c. VA facility's Privacy Officer (PO – Angela Pluff, ext. 53784, Angela.Pluff@va.gov)
d. VA facility's Security Officer (VA Police Chief, ext. 53333)

(3) Notify others such as the Medical Center Director (James Cody, ext. 54895) or the Chief of Staff (William Marx, ext. 54888).

b. The ACOS for R must report the research events listed in subparagraphs 6b and 6c to the Facility Director and the R&D Committee as soon as possible, but no later than 5 business days after becoming aware of them.

c. An RCO identifying and confirming serious or continuing noncompliance during an ORO-mandated informed consent or regulatory audit, must report the noncompliance to the Facility Director, the IRB and/or the IACUC, the ACOS for R, and the R&D Committee as soon as possible, but no later than 5 business days after becoming aware of them. Where applicable, simultaneous reports must be made to the facility ISO, PO, and/or relevant research oversight committee. The Facility Director must then report to ORO Regional Office (RO) at VHANortheastRegionalOfficeofResearchOversight@va.gov Network Office, and the Office of Research and Development (ORD) as soon as possible, but no later than 5 business days after being notified by the RCO. If the IRB ultimately determines that serious or continuing noncompliance actually did occur, Facility Director must report promptly to OHRP and/or FDA.

d. **Reports to ORO ROs.** The Facility Director must report the following research events to the appropriate ORO RO as soon as possible, but no later than 5 business days after being informed of them (see App. A, Table 1).

(1) **Serious or Continuing Noncompliance.** Any serious or continuing research-related noncompliance with VA or other Federal requirements pertaining to information security or privacy (e.g., 45 CFR 160 and 164, VA Directive 6502, VA Handbook 6500, VHA Handbook 1605.1).

(2) **Unauthorized Activities.** Any unauthorized, research-related access, use, disclosure, transmission, removal, theft, or loss of VA sensitive information, including, but not limited to: protected health information, individually-identifiable private information (as defined in 38 CFR 16.102(f)(2)), confidential information, and Privacy Act-protected information.

(3) **Other Incidents.** Any research-related incidents reportable to the Office of Information and Technology (OI&T) Network and Security Operations Center (NSOC). ***NOTE:*** *Research personnel must adhere to all VA OI&T NSOC requirements, including those under which certain incidents be reported immediately. Research personnel must simultaneously provide such reports to the ACOS for R.*

(4) **External Noncompliance Findings.** Any findings of noncompliance related to research information security or privacy by any VA office, any other Federal department or agency, or any other entity. The Facility Director's report to ORO must include a copy of the entity's official findings.

e. **Reports to ORO Central Office.** As soon as possible, but no later than 5 business days after being informed of any substantive change in an MOU or System Interconnection Agreement (SIA) with an affiliate institution or other entity related to research information security or research privacy arrangements, the Facility Director must report the change to ORO Central Office, with a copy to the appropriate ORO RO (see App. A, Table 2).

7. REQUIREMENTS RELATED TO RESEARCH MISCONDUCT

a. **Procedures.** The full procedures for handling research misconduct allegations are found in R&D SOP 151-07.

8. REFERENCES

VHA Directive 1058.01, Requirements For Reporting Research Events To Facility Oversight Committees And The Office Of Research Oversight.

05.08/10

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Appendix A
SUMMARY OF REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO THE OFFICE OF RESEARCH OVERSIGHT (ORO)

Table 1. Reports to ORO Regional Offices with a Copy to the VISN2 Network Office*

Human	Information Protection
1. Problems involving risks to subjects or others that are unanticipated and serious and related, or possibly related, to the research, including work-related injuries; interruptions in research activities due to concerns about the safety, rights, or welfare of subjects, staff, or others; and data Monitoring Committee reports or sponsor analysis describing a safety problem. 2. Local adverse events that are unanticipated and serious and related, or possibly related, to the research. 3. Serious or continuing noncompliance as determined by the Institutional Review Board (IRB) or identified by a Research Compliance Officer (RCO) audit, including findings of external entities. 4. Suspensions or terminations of IRB approval related to concerns about the safety, rights, or welfare of subjects, staff, or others, including suspensions by the IRB of new enrollments or other research activities.	1. Any serious or continuing noncompliance with VA or other Federal requirements. 2. Any unauthorized, research-related access, use, disclosure, transmission, removal, theft, or loss of protected health information, individually identifiable private information, confidential information, Privacy Act protected information, or other VA sensitive information. 3. Any research-related incidents reportable to the Office of Information and Technology (OI&T) Network and Security Operations Center (NSOC). 4. Findings of noncompliance by external entities.

****NOTE:** *Members of the VA research community, including RCOs, must notify the Associate Chief of Staff for Research and relevant oversight committee as soon as possible but no later than 5 business days after becoming aware of these events. The Facility Director must notify ORO in writing as soon as possible but no later than 5 business days after being informed of these events.*

SUMMARY OF REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO ORO

Table 2. Reports to ORO Central Office (with copy to ORO Regional Office and VISN) *

Human	Information Protection
1. Any change in the facility's Federalwide Assurance (FWA) or other ORO-approved Assurance, 2. Any change in the facility's designated IRB(s). 3. Any change in an memorandum of Understanding (MOU) related to the designation of IRBs or other human research protection arrangements. 4. Failure of the VA facility to achieve "full accreditation" status from the VA human research accreditation organization, any change in the facility's accreditation status, or any change in the accreditation status of an affiliate involved in the facility's human research protection program.	1. Any change in an MOU or System Interconnection Agreement related to research information security arrangements.

****NOTE:** *Members of the VA research community, including RCOs, must notify the ACOS for Research and relevant oversight committee as soon as possible, but no later than 5 business days after becoming aware of these events. The Facility Director must notify ORO in writing as soon as possible, but no later than 5 business days after being informed of these events.*

ADVERSE EVENTS IN RESEARCH AS UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS

1. Federal Policy. The Federal Policy (Common Rule) for the Protection of Human Subjects and Department of Veterans Affairs (VA) regulations at Title 38 Code of Federal regulations (CFR) 16.103(b)(5) require written procedures for promptly reporting the following to the Institutional Review Board (IRB), institutional officials, and the Department or Agency Head:

a. Unanticipated problems involving risks to subjects or others.
b. Serious or continuing noncompliance with regulatory requirements or IRB requirements or determinations.
c. Suspensions or terminations of IRB approval.

2. Food and Drug Administration (FDA) IRB Regulations. FDA IRB regulations at 21 CFR 56.108(b)(1) contain the identical reporting requirements.

3. FDA Device Regulations. FDA device regulations at 21 CFR 812.150(a)(1) require that the investigator report serious unanticipated adverse device effects to the IRB no later than 10 business days after the investigator first learns of the effect.

4. FDA Drug Regulations. Neither the VA human subject protection regulations (38 CFR 16, Common Rule) nor the FDA investigational new drug regulations at 21 CFR 312 contain explicit requirements for promptly reporting adverse drug events to the IRB when the adverse drug events do not constitute unanticipated problems involving risks to subjects or others.

5. VHA Policy Requirements. VHA Handbook 1200.5 indicates that individual data and safety monitoring plans for reporting Adverse Events (AEs) to the IRB may vary depending upon the potential risks, complexity, and nature of the study. VHA Handbook 1200.5 requires that the IRB establish written procedures for notifying medical center officials and VA Central Office of any AEs that cause "harm or risk of harm to human subjects or groups."

6. AEs as Unanticipated Problems. Except for serious, unanticipated adverse device effects, Federal regulations require that AEs be reported promptly to the IRB only when they constitute unanticipated problems involving risks to subjects or others.

7. Unanticipated Problems versus AEs. Unanticipated Problems Involving Risks (UPRs) to subjects or others and AEs constitute overlapping, but not identical, concepts (see Figure 1 of App. B).

a. UPRs may include both risks to subjects and risks to other individuals (e.g., research personnel, subjects' family members). Risks may reflect any type of potential harm (e.g., physical, psychological, social, economic, and breach of privacy).

b. UPRs include some (but not all) AEs, and AEs include some (but not all) UPRs.

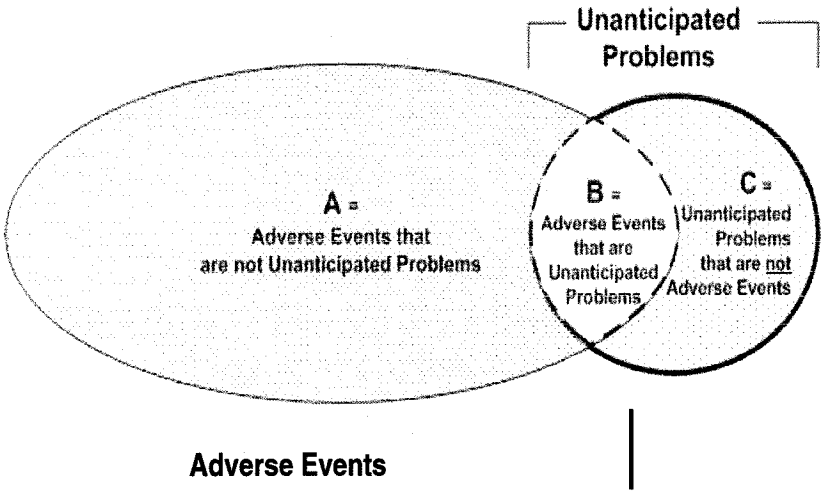

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Figure 1. UPRs and AEs constitute overlapping, but not identical, concepts. *UPRs include some (but not all) AEs, and AEs include some (but not all) UPRs.*

8. AEs That Are Not UPRs. Examples include the following situations:

a. A subject experiences soreness and redness at the investigational drug injection site that are consistent in nature, severity, and frequency of occurrence with anticipated side effects described in the IRB-approved protocol and consent document.

b. A subject experiences anxiety and stress (in response to interview questions about a traumatic event) that are consistent in nature, severity, and frequency of occurrence with anticipated reactions described in the IRB-approved protocol and consent document.

9. AEs That Are UPRs. Examples include the following situations:

a. A subject experiences soreness and redness at the investigational drug injection site that are more severe than anticipated side effects described in the protocol and consent document.

b. More subjects than anticipated in the protocol and disclosed in the consent document experience anxiety and stress in response to interview questions about a traumatic event.

c. Two hours after receiving an investigational drug, a subject experiences intense headache and vomiting that last about an hour and then resolve. Neither was described in the protocol or consent document as a possible side effect of the research.

10. UPRs That Are Not AEs. Examples include the following situations:

a. A subject mistakenly receives twice the dose of an investigational drug than was stipulated in the protocol, but suffers no side effects and no indication of harm.

b. A subject receives one dose of active drug instead of placebo but suffers no side effects and no indication of harm.

c. A laptop containing identifiable private information is stolen from a research lab but is recovered from a campus dumpster several hours later. Data files remain intact.

d. A research assistant suffers a severe burn due to malfunctioning research equipment.

e. During an interview about children's play, a parent-subject confesses a continuing problem with child abuse. Materials approved by the IRB did not address how such situations would be handled.

f. The investigator receives a Data Monitoring Committee (DMC) report indicating that researchers should look out for a particular side effect that may be occurring more frequently than anticipated.

g. The sponsor suspends new enrollments in a trial due to suspected manufacturing problems.

h. New studies in the published literature suggest that the drug being used in a research study may be associated with a previously unknown risk of stroke.

11. Requirements for Reporting to the IRB. UPRs must be reported to the IRB in accordance with VA's codification of the Common Rule at 38 CFR 16.103(b)(5) and subparagraph 6a(3) of the Handbook.

a. Local SAEs and problems involving risks to subjects, or others, must be reported to the IRB and the Associate Chief of Staff for Research within 5 business days utilizing the Serious Adverse Event Report Form.

b. Figure 2 (next page) of Appendix B provides a "yes/no" decision chart to identify situations involving problems and SAEs that must be reported to the IRB.

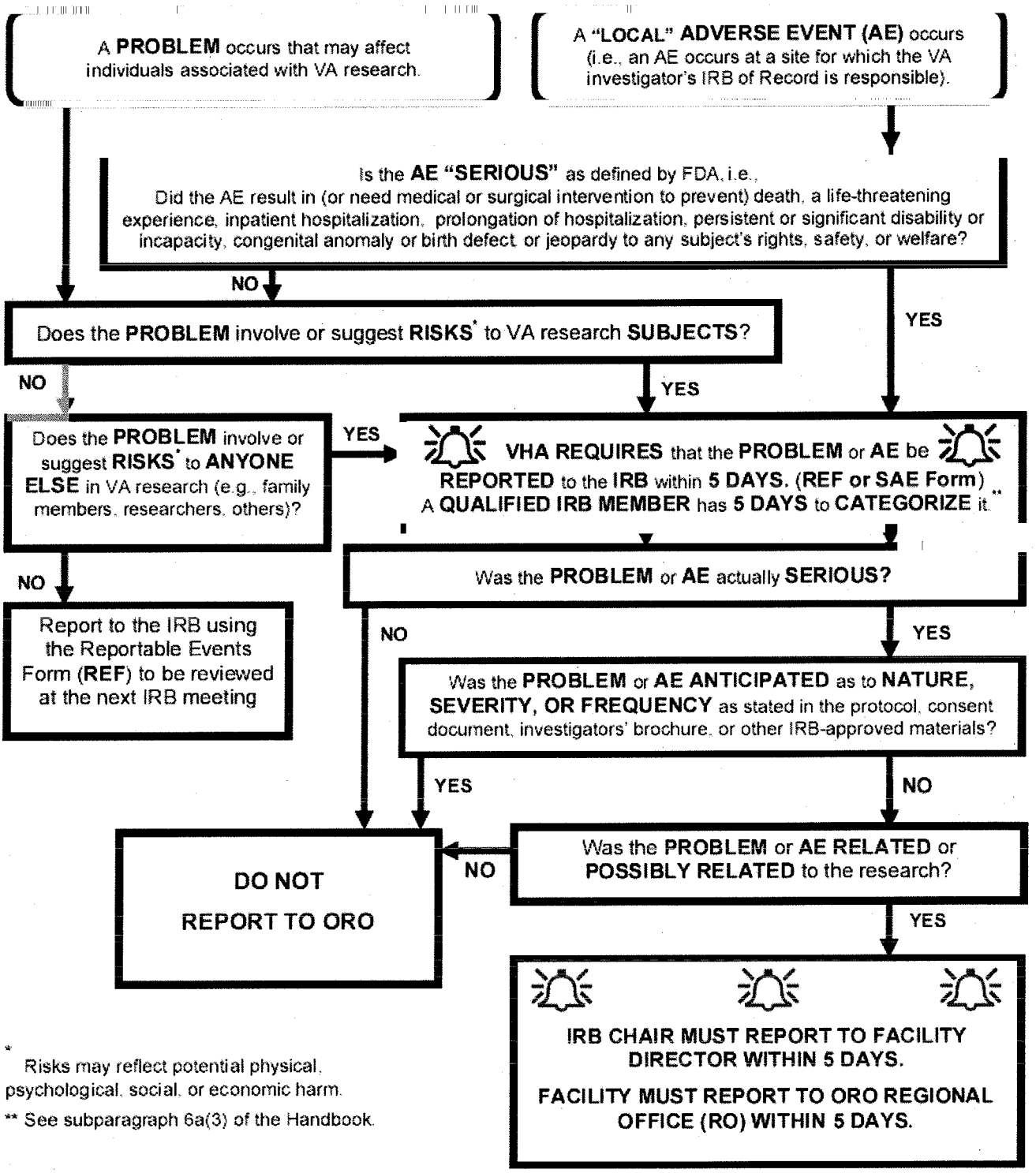

Figure 2. Decision chart for reporting UPRs and AEs to the IRB and ORO. *Reports should be sent to the appropriate ORO Regional Office.*

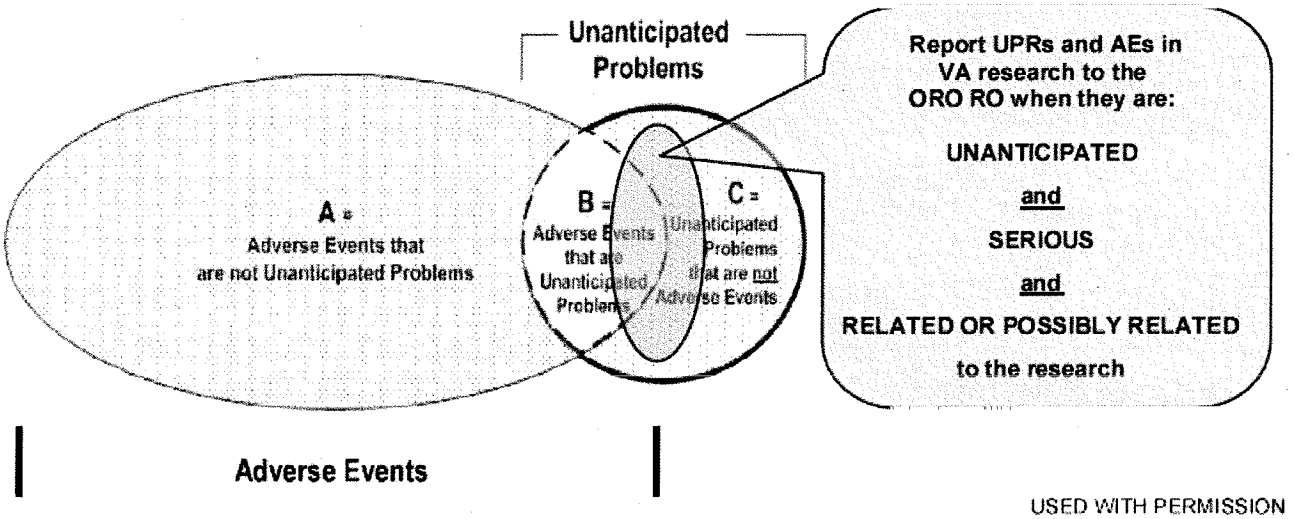

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Figure 3. UPRs, including certain AEs, must be reported to ORO. *Reports need to be sent to the ORO RO responsible for oversight of the facility when the UPRs or AEs: (a) Occur at a VA facility or in research conducted by individuals acting as VA employees, and (b) Are found by the IRB to be unanticipated and serious and related to the research.*